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Predictive Value for Future Arrhythmic Events of Fractal Dimension, a Measure of Time Clustering of Ventricular Premature Complexes, After Myocardial Infarction

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Objectives. **Our objective was to test fractal dimension (D), a measure of clustering of ventricular premature complexes (VPCs), on entry Holter recording as a predictor of future arrhythmic death and other-cause mortality in postinfarction patients in the Cardiac Arrhythmic Suppression Trial (CAST).**

Background. **Nonlinear dynamic methods of signal processing are being applied in medicine to provide new insights into apparently "chaotic" biologic events, including cardiac arrhythmias. One such application is the derivation of a fractal D to describe the clustering of VPCs in time.**

Methods. **Baseline Holter recordings were analyzed in blinded manner for 484 patients: 237 died or had a resuscitated cardiac arrest during follow-up, and 247 matched patients had no events. Fractal D, measured in four ways, was assessed as a predictor using Cox regression.**

Results. **One measure of D (high resolution D) was a significant univariate (relative hazard ratio 0.79 per SD change, p = 0.011) and multivariate (hazard ratio 0.75, p = 0.046) predictor of arrhythmic death but not other death (univariate p = 0.95, relative hazard 0.95, p = 0.66). Fractal D was greater (VPCs less clustered) in those patients free of arrhythmic events. On subgroup analysis, the predictive value of D resided in the randomized patient group (i.e., those who showed VPC suppression during initial antiarrhythmic drug titration and were randomized to blinded therapy with active drug or placebo) (multivariate hazard ratio 0.57, p = 0.001).**

Conclusions. **A high resolution fractal D was predictive of arrhythmic (but not nonarrhythmic) death in a large postinfarction cohort. Further study of this new signal processing approach to ambulatory electrocardiographic recording will be of interest.**

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Ambulatory electrocardiographic (ECG) recording (Holter monitoring) has been extensively used for detection, risk stratification and therapeutic guidance of ventricular and supraventricular arrhythmias. Information derived from Holter monitoring commonly includes the frequency of single ventricular premature complexes (VPCs), couplets and runs of ventricular tachycardia. Together with markers of left ventricular dysfunction, the frequency and complexity of ventricular arrhythmias have been used as prognostic indicators in patients with structural heart disease, including myocardial infarction (1–3). However, arrhythmia frequency by itself is an imperfect marker of risk, and suppression of prognostically important ventricular arrhythmias does not necessarily predict an improved prognosis (4–6). Hence, other measures of vulnerability to life-threatening ventricular arrhythmias are of interest. Examples of advanced approaches to ECG signal processing include signal averaging (7,8), heart period variability (9) and fractal dimension (D) measures of VPC clustering (10).

Deterministic chaos is a term applied to the seemingly unpredictable behavior that may arise in response to the internal feedback loops of nonlinear systems. "Chaos theory," using the mathematics of nonlinear dynamics, has recently been applied to assess the complexity of biologic systems, including the cardiovascular system, enabling measurement of the output of physiologic systems that generate highly variable fluctuations resembling "chaos," in which output is not proportional to input (10–18). The frequency distributions of heart rate and ventricular arrhythmias over time exemplify two candidate cardiovascular response systems that may be analyzed using nonlinear dynamics.

Fractals are a class of geometric patterns that are irregular but have underlying self-similarity, often on multiple scales, that classic Euclidean geometry is unable to characterize (11). The frequency distribution over time of VPCs is a candidate fractal system. Nonlinear dynamics allow derivation of a fractal

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Abbreviations and Acronyms

CAST = Cardiac Arrhythmia Suppression Trial
D = dimension (fractal)
ECG = electrocardiogram, electrocardiographic
ln = natural logarithm
log = logarithm
VPC = ventricular premature complex

D to describe systems showing fractal geometry (11), a specific application of deterministic chaos theory (12,13).

This study tested the predictive values for future cardiovascular events and, in particular, arrhythmic events, of estimates of fractal D as descriptors of the degree of clustering of VPCs over time in patients with recent myocardial infarction and ambient ventricular ectopy who entered and were followed up in the Cardiac Arrhythmia Suppression Trial (CAST) (4–6,19).

Methods

Study objectives. The main objective of the study was to determine whether measures of clustering of VPCs in time, as recorded on a 24-h baseline ambulatory monitor tape and described by a fractal D (determined by one of several methods of signal processing), could be used to identify postinfarction patients at increased risk for sudden death/cardiac arrest (primary hypothesis) or all-cause death/cardiac arrest (secondary hypothesis) within the CAST study group.

Patient selection criteria. General entry criteria for CAST and treatment strategies have been previously reported (4–6). In brief, patients were required to have had a documented acute myocardial infarction within 6 to 90 days of study entry, together with a left ventricular ejection fraction ≤55%, or acute myocardial infarction within the window of 90 days to 2 years, coupled with an ejection fraction ≤40%. In addition, baseline ventricular ectopy was required (VPC frequency averaging ≥6/h on a 24-h ambulatory ECG monitor). Patients with runs of ventricular tachycardia ≥15 beats at rate ≥120 beats/min were excluded.

In addition to receiving standard, physician-directed therapy, patients were randomized to receive encainide, flecainide or moricizine therapy, and suppressibility of VPCs was tested. When a drug and dose were found to be effective (achieving ≥80% VPC suppression) or partially effective, the patient was randomized to long-term therapy with active drug or matching placebo. When none of the tested drugs and doses was effective or tolerated, the patient was not randomized but was followed outside of the main CAST study. A total of 3,549 patients were entered into CAST-I or CAST-II (19). Suppression of arrhythmias was achieved in 2,491 patients and partial suppression in 260 patients, and 635 patients were not randomized to long-term, blinded use of the study drug because of failure to achieve even partial suppression or intolerance or because of miscellaneous reasons. Event rates assessed during long-term clinical follow-up were those for arrhythmic death plus resuscitated cardiac arrest and all-cause death plus resuscitated cardiac arrest.

Selection of patients and control subjects. Patients were selected for study if they were entered into CAST, had an analyzable baseline 24-h ambulatory Holter monitor recording with at least 200 VPCs, were followed long-term and if they died (of any cause) or had a resuscitated cardiac arrest during follow-up (n = 237). An approximately equal number of CAST patients (n = 247) who did not have events during follow-up were selected as control subjects, matched by site and selected to have approximately similar distributions of important risk factors as well as treatment assignment (active drug vs. placebo) and study group status (randomized vs. nonrandomized).

The randomized group ("VPC suppressible") included 301 patients—145 patients with an event during follow-up and 156 control subjects without an event. The nonrandomized group included 183 patients—92 patients with an event and 91 control subjects without an event.

Holter tapes from all patients with events and from control subjects were selected at the central CAST Coordinating Center (Seattle) and sent to the Fractal Analysis Laboratory (Salt Lake City) for processing.

Computing fractal D. Fractal D was determined by signal processing of the baseline 24-h Holter recordings at the core laboratory in a manner blinded to patient characteristics, treatment assignment, suppression status and patient outcome. Computed values for fractal D were then sent back to the Coordinating Center and incorporated into the CAST data base.

Holter recordings taken at the individual CAST study sites were scanned for VPCs at the core laboratory using an operator-interactive system (Marquette), and the timing of each VPC from the beginning of the tape was identified to within 8 ms and entered into an annotated computer file. The annotated files of the recordings were then used for estimation of fractal D using the correlation technique of Grassberger and Procaccia (20), as previously described (21–23). Three estimates for D used a custom-designed program (K.M.S.) to identify all possible VPC pairs within times of one another ranging from ≤1 to ≤10 min and the time-distance between them was sorted into 30-s increments (21). (This analysis was computationally efficient but induced potential lumping and roundoff error into the estimation of the time interval of VPC pairing: it looked at intervals between 1 and 10 min but ignored shorter [<1-min] intervals.)

These three estimates are described:

Initial D. Fractal D was based on the first 200 VPCs only on the tape. This method has been previously reported (10), is straightforward, uniformly applicable and least time-consuming, but D is based on the least information of the methods.

Minimal D. The minimal D was selected from all Ds determined on 200 consecutive VPC analyses throughout the Holter tape. This "worst case" (most clustered) D determination throughout the 24 h was tested as a possibly better predictor for events.

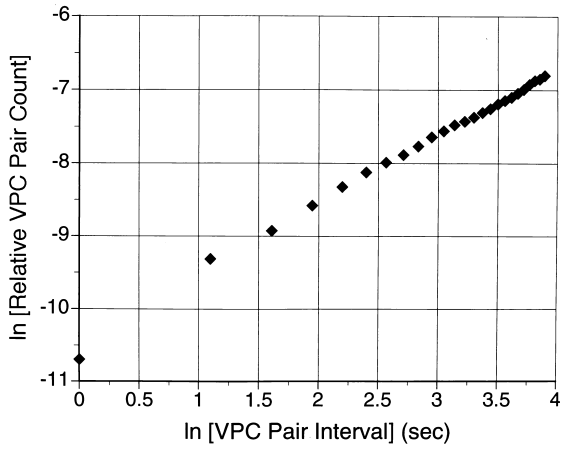

Figure 1. Graphic example of fractal D (high resolution D) determined as the slope of the plot of ln (relative VPC pair count) versus ln (VPC pair interval) (in seconds) (see Methods for details). Note strong terminal linearity of plot. For this patient, D = 0.949 and r = 0.998.

Median D. The median D was selected from all Ds determined by 200 consecutive VPC analyses throughout the Holter tape. This more representative (median) D was tested to see whether it would be a still more accurate predictor of arrhythmic risk.

For these measures, the logarithms of VPC pair counts (C) for each time distance were then correlated with the logarithms of the respective time distance (r) using linear regression. The slope (D) of the correlation line ($\log C = a + D \log r$) was taken as the correlation dimension, designated as fractal D. (If VPCs are distributed uniformly over time, D is greater [i.e., values are near 1], whereas densely clustered VPCs yield a smaller D, nearer to 0.)

High resolution D. This fourth (new) estimate differed in two ways: 1) All VPCs throughout the Holter recording were used in the analysis; and 2) VPC pairing was sorted to within a more precise time interval (i.e., to within 1 s) than that obtained by the other methods (i.e., only to within 1 min). Specifically, the time interval for analysis of VPC pairings began with 1 s and was increased by 2-s intervals up to a maximal interval of 49 s. (These time intervals were chosen empirically [L.A.K.] because it appeared intuitively more likely that VPCs paired at short time intervals—that is, in seconds—would interact to predict arrhythmic risk more than pairings at long time intervals—minutes to hours. However, the analysis was much more computer demanding.) Thus, for each "r" time interval ranging from 1 to 49 s, the number of VPC pairs that occurred throughout the tape was counted ("total count"). The relative pair count (C[r]) associated with each "r" interval was then computed as the total count for that "r" divided by the square of the number of VPCs in the entire tape. Then, high resolution D is the slope of the line relating log (relative counts) to log (interval lengths)—that is, $\log C(r) = a + \beta \log (r)$, determined by linear regression using the method of least squares (24,25). A graphic example is given in Figure 1. Linear regression yielded excellent correlation coefficients (average [±SD] r = 0.97 ± 0.03, sample n = 57).

In a computer-based feasibility and comparability study, high resolution D and median D were assessed by one of us (K.M.S.) for their ability to estimate true D by using a series of computer-simulated VPC sets. The high resolution D algorithm gave excellent approximations of theoretic (computer-generated) fractal Ds, with a correlation coefficient between theoretic and calculated values of 0.97 for VPC sets >200 (as in our study), although it tended to slightly but systematically overestimate D (i.e., by giving values of D slightly over 1). In contrast, the median D algorithm yielded estimates that showed a poorer correlation with theoretic D (correlation coefficient 0.85) and systematically underestimated true D.

Statistical approach to risk analysis. Univariate and multivariate Cox regressions (26) were performed for each estimate of D, with D entered as a continuous variable, for predicting survival to 1) arrhythmic death or resuscitated cardiac arrest; 2) nonarrhythmic death; and 3) total (all-cause) death or resuscitated cardiac arrest. Statistical (p) value limits for removing and entering variables from the stepwise model were 0.15 and 0.10, respectively. Six covariates were prospectively selected as candidate predictors and were entered along with fractal D in the stepwise multivariate analyses: age, gender, natural logarithmic (ln) VPC/h, ejection fraction, history of congestive heart failure and randomization status (VPCs "suppressible," patient randomized to blinded antiarrhythmic drug or placebo: yes/no), and, in randomized patients, drug treatment status (active or placebo). No correction in p values for the multiplicity of fractal D analyses, thought to be correlated estimates of the same underlying measure, were made.

The first analysis assessed fractal D as a predictor in all Holter-evaluable patients with events compared with their respective control subjects. The secondary analyses evaluated the predictive value of D and other baseline factors in the two distinct subgroups: 1) the "randomized" group: patients were randomized to "effective" (or partially effective), blinded therapy or to placebo. These patients were followed in the main CAST studies; 2) the "nonrandomized" group: antiarrhythmic drug testing was ineffective or not tolerated. Patients were not randomized to therapy and were followed outside of the main CAST studies.

Results

Baseline characteristics. Selected baseline characteristics of the overall study group and subgroups are presented in Table 1. Patients (with death or resuscitated cardiac arrest) and control subjects (without events) were well matched, except that patients had a shorter duration of follow-up (as expected) and somewhat more commonly had a history of heart failure (p = 0.02). Patients in the nonrandomized group were slightly older (p = 0.081), had a higher incidence of heart failure (p = 0.037), a higher rest heart rate (p = 0.0056) and tended to have a lower ejection fraction (p = 0.058), but had fewer VPCs/h (p = 0.047) and a shorter average follow-up (exposure) time.

Table 1. Baseline Characteristics by Randomization and Therapy Group Status

Characteristic	Total (n = 484)	Case (n = 237)	Control (n = 247)	Nonrandomized (n = 183)	Active (n = 157)	Placebo (n = 144)
Death/CA status						
Event	237	237	0	92	72	73
Censored	247	0	247	91	85	71
Arrhythmic death/CA						
Event	130	130	0	55	40	35
Censored	354	107	247	128	117	109
Male (%)	81	78	83	81	78	83
Age (yr)	64.1	64.4	63.8	65	63.7	63.5
Exposure (mo)	21.8	13.8	29.5	12.3	27.3	28
ln VPCs/h (base)	4.18	4.26	4.1	4.04	4.35	4.17
Ejection fraction (%)	28.3	27.5	29.1	27.2	27.8	30.4
Heart rate (beats/min)	77.8	78.7	76.9	79.7	76.1	77
Previous CHF (%)	31.0	35.9	26.3	36.6	30.6	24.3
Initial fractal D	0.863 ± 0.15	0.87	0.855	0.874	0.851	0.86
Minimal fractal D	0.758 ± 0.19	0.769	0.747	0.783	0.736	0.749
Median fractal D	0.898 ± 0.10	0.904	0.892	0.907	0.888	0.897
High resolution fractal D	1.083 ± 0.29	1.064	1.102	1.052	1.106	1.098

CA = cardiac arrest; CHF = congestive heart failure; D = dimension; ln = natural logarithm; VPCs = ventricular premature complexes.

Four estimates of fractal D. Average estimates of D, using each of the four methods, are presented in Table 1 for all patients and for the randomization subgroups. As expected, average minimal D was lower than initial D or median D. Average high resolution D values were found to be higher than values determined by the other methods. Values for minimal D ($p = 0.018$) and high resolution D ($p = 0.066$) also differed by randomization status.

The first three estimates of D were significantly correlated ($r = 0.56$ to 0.75) and had relatively large coefficients of variation (SD/mean): 4.3, 6.3 and 9.1 for minimal, initial and median D, respectively. Moreover, none predicted risk univariately or multivariately. High resolution D was not correlated with any of these first three estimates and had a smaller coefficient of variation—3.8. The subsequent discussion focuses on high resolution D.

High resolution D as a univariate predictor in the overall group. High resolution D was a significant univariate predictor of events in the overall group in the Cox regression analysis.

Table 2. Univariate Predictive Value of High Resolution Dimension in Cox Regression Model By Therapy Group Status

Outcome Measure	Overall Group	Randomized Patients	Nonrandomized Patients
Arrhythmic death/CA			
Coefficient	−0.8008	−1.4278	—
Chi-square	6.51	11.14	0.23
p value	0.011	0.001	0.63
Nonarrhythmic death			
Chi-square	0.00	0.10	0.02
p value	0.95	0.76	0.88

Values represent global chi-square and p values for overall group and randomized patients and entry chi-square and p values for nonrandomized patients.

For arrhythmic death/cardiac arrest, the primary outcome of interest, D yielded a global chi-square of 6.51 ($p = 0.01$) (Table 2). The relative hazard ratio for high resolution D was 0.79 per SD separation in high resolution D. Fractal D was greater (VPCs less clustered) in event-free patients (1.102 ± 0.02 [SEM]) than in those with arrhythmic events (1.033 ± 0.02). However, D did not discriminate nonarrhythmic death, averaging 1.102 ± 0.02 in event-free patients and, similarly, 1.102 ± 0.03 in those with events.

Multivariate predictors in the overall group. Four variables, including total D, were entered into the Cox multivariate predictive model of arrhythmic death/cardiac arrest (Table 3): randomization status (i.e., VPCs "suppressible," patient randomized to drug or placebo: yes/no) ($p < 0.001$), ejection fraction ($p = 0.010$), high resolution D ($p = 0.046$) and ln VPC/h ($p = 0.016$). The multivariate relative hazard ratio for high resolution D was 0.79 per SD. (History of heart failure did not achieve significance as a univariate predictor of arrhythmic death/cardiac arrest [$p = 0.08$], and its predictive power was further reduced by the entry of ejection fraction into the multivariate model.)

Two variables, not including high resolution D, were entered into the Cox multivariate predictive model of nonarrhythmic death (Table 4): randomization status ($p < 0.002$) and age ($p < 0.001$). The hazard ratio for high resolution D was 0.95 ($p = 0.66$).

For combined events (total death), randomization status ($p < 0.001$), ejection fraction ($p = 0.003$), ln VPC/h ($p = 0.039$) and high resolution D ($p = 0.018$) were entered.

Univariate prediction in randomized patients. Given the importance of randomization status as a predictor of events, we next evaluated whether high resolution D was specifically of predictive value in randomized ("suppressible") patients. (Indeed, a significant [$p = 0.01$] interaction between randomiza-

Table 3. Multivariate Cox Regression Model of Arrhythmic Death/Cardiac Arrest

Step No.	Variable Entered	DF	Log Likelihood	Improvement Chi-Square	p Value	Global Chi-Square	p Value	Coefficient
0			−746.5					
1	Randomization status	1	−737.3	18.45	<0.001	20.38	<0.001	−0.8237
2	EF	2	−734	6.72	0.01	26.6	<0.001	−0.0182
3	High resolution D	3	−732	3.99	0.046	30.46	<0.001	−0.9786
4	ln VPCs/h	4	−729.1	5.79	0.016	36.34	<0.001	0.1977

Seven variables were considered in the stepwise model: high resolution dimension, age, gender, natural logarithmic ventricular premature complexes, ejection fraction, history of heart failure and randomization status (qualified, received blinded therapy: yes/no). Statistical (p) values for removal and entry were 0.15 and 0.10, respectively. DF = degrees of freedom; EF = ejection fraction; other abbreviations as in Table 1.

tion status and predictive value of high resolution D for arrhythmic death/cardiac arrest was found on analysis of variance for the total patient group.)

High resolution D was a highly significant univariate predictor in the randomized patient group in the Cox regression analysis (Table 2). For arrhythmic death/cardiac arrest, the relative hazard ratio was 0.66 and global chi-square 11.14 ($p = 0.001$). Fractal D was greater (VPCs less clustered) in event-free patients (1.134 ± 0.02 [SEM]) than in those with events (1.006 ± 0.03). Two-thirds of patients with arrhythmic events had "low" (less than median) total D ($p < 0.001$) compared with less than one-half of patients without events (Fig. 2).

In contrast, D did not predict nonarrhythmic death: global chi-square 0.10 ($p = 0.756$). Fractal D averaged 1.134 ± 0.04 in those with nonarrhythmic events, and, similarly, 1.134 ± 0.02 in event-free patients.

Predictive value of high versus low fractal D. Sensitivity of "low" versus "high" high resolution D (Fig. 2) for an arrhythmic event or death was 64%, specificity 53%, positive predictive value 31%, negative predictive value 82% and overall predictive accuracy 56%.

Multivariate predictors in randomized patients. Three variables were entered into the Cox multivariate model as predictors of risk of arrhythmic death/cardiac arrest: high resolution D ($p = 0.001$), relative hazard ratio 0.57, ln VPC/h ($p = 0.010$) and age ($p = 0.072$).

One variable, age ($p = 0.027$), was entered into the multivariate model as a predictor of risk of nonarrhythmic death.

Predictors in nonrandomized patients. High resolution D was neither a univariate (Table 2) nor multivariate predictor in the nonrandomized patient group. For this group, the multivariate model selected only a history of congestive heart failure ($p = 0.045$) as a predictor of arrhythmic death/cardiac arrest and age ($p = 0.008$) as a predictor of nonarrhythmic death.

Discussion

Synthesis of overall findings. Among postinfarction patients with ventricular ectopy and left ventricular dysfunction who qualified for the CAST study and were followed for up to 3 years, high resolution D was found to be a significant univariate and multivariate predictor of arrhythmic death or cardiac arrest, adding to the predictive value of VPC frequency alone, with D being smaller (VPCs more clustered) in patients with arrhythmic events than in those with no events or nonarrhythmic events.

An additional finding was the interaction between randomization status and high resolution D for arrhythmic events: D was predictive in randomized (VPC suppressible) but not in nonrandomized (nonsuppressible) patients. (In contrast, although the adverse mortality effects of active drug therapy with encainide, flecainide and moricizine after an infarction were well demonstrated by CAST [4–6], assignment to active drug versus placebo therapy did not interact with the predictive value of fractal D.) Nonrandomized patients differed from randomized patients at baseline in several important respects: they were older, had a higher incidence of heart failure, had lower ejection fractions and had higher rest heart rates, but fewer VPCs. Nonrandomized patients thus were sicker, with poorer ventricular function, arrhythmias unresponsive to therapy and mortality risk perhaps almost exclusively determined by ventricular dysfunction. In any event, fractal D was not a useful predictor in patients selected by their unresponsiveness to antiarrhythmic therapy. Suppressibility as a marker of good prognosis (and nonsuppressibility of poor prognosis) has been

Table 4. Multivariate Cox Regression Model of Nonarrhythmic Death

Step No.	Variable Entered	DF	Log Likelihood	Improvement Chi-Square	p Value	Global Chi-Square	p Value	Coefficient
0			−591.344					
1	Age	1	−585.035	12.60	<0.001	11.617	0.001	0.0422
2	Randomization status	2	−580.091	9.89	0.002	22.496	0.000	−0.6940

Seven variables were considered in the stepwise model: high resolution dimension, age, gender, natural logarithmic ventricular premature complexes, ejection fraction, history of heart failure and randomization status (qualified, received blinded therapy: yes/no). Statistical (p) values for removal and entry were 0.15 and 0.10, respectively. DF = degrees of freedom.

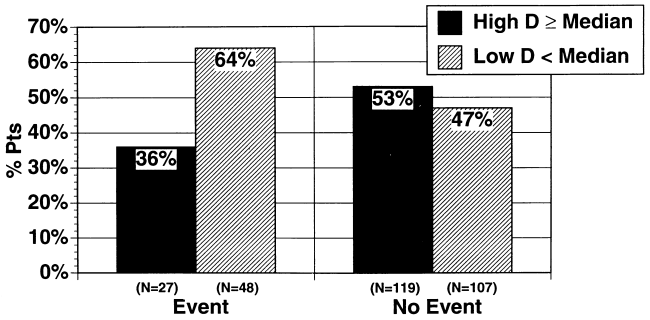

Figure 2. Distribution of high resolution D values above and below the median (1.102) in patients (Pts) with and without subsequent arrhythmic death or resuscitated cardiac arrest during follow-up. The difference in D values between the groups was significant by both analysis of variance ($p = 0.0009$) and simple chi-square analysis ($p = 0.01$) of values dichotomized at the median.

previously noted in the CAST (and other) postinfarction cohorts (4–6,27–30).

Variability in predictive value of fractal D measures. Only one of the two essentially different approaches to estimating fractal D (i.e., high resolution D) was predictive in the CAST group. The first three estimators were highly correlated with each other but showed high noise/signal ratios (large variances) and were unpredictive of events.

Uniquely, high resolution D takes into account all VPCs throughout the 24 h of recording and analyzes all possible pairings at short to intermediate times (<1 to 50 s). The results showed that this estimate of D added independently to the predictive value of ln VPC frequency in multivariate modeling, especially for fatal arrhythmic events. (The association of D and ln VPCs was weak [$r = 0.41$, data not shown].) This result suggests that the pattern of VPC pairings at short time intervals—seconds—predicts risk of arrhythmic events better than at long time intervals—minutes to hours—and may be important to the predictive accuracy of fractal D determination.

Comparisons with other studies. The application of nonlinear dynamic methods such as fractals to cardiac rhythm disorders is still in its infancy. Stein and Kligfield (10) retrospectively examined ambulatory ECG data in 18 patients with severe ischemic or nonischemic dilated cardiomyopathy who had been followed from the time of monitoring for as long as 4 years. A difference in survival ($p < 0.002$) was observed when fractal D (determined on the initial 200 VPCs, comparable to "initial D") was separated at the median value. Patients with a higher D (less clustered) showed better survival at 6 months, with differences closing by 24 months.

This measure of fractal D also was evaluated as a prognostic marker in 39 patients with advanced valvular heart disease (severe mitral insufficiency) and >200 VPCs/day (22). Patients were classified according to ventricular performance (left and right ventricular ejection fractions ≤45% or >45% and ≤30% or >30%, respectively) and fractal D (divided at the median value). An excess of sudden deaths was observed in those with poor performance and clustered VPCs compared with poor performance and uniform VPCs (four of seven vs. one of five, $p = 0.02$). No deaths occurred in those with good ventricular performance.

Preliminary findings on the predictive value of fractal D in patients being treated for life-threatening ventricular arrhythmias also has been recently reported in 105 patients (31). Only fractal D and sotalol therapy (vs. class I drugs) were found to be independent predictors for arrhythmia recurrence among 10 baseline and treatment variables.

In contrast to these positive results, a preliminary study in postinfarction patients with ventricular ectopy enrolled in the Cardiac Arrhythmia Pilot Study (CAPS) failed to find "initial" fractal D (determined on the first 200 VPCs) to be predictive of outcome (32). The present, expanded study from CAST confirms this negative result for "initial D" in the postinfarction cohort but indicates that another estimate, high resolution D, may be predictive.

Study strengths and limitations. This analysis used a large data base (484 events among 3,549 patients) in a carefully and prospectively studied population (CAST). The substudy hypothesis and plan were defined prospectively, before analysis was undertaken, and fractal Ds were estimated at a core laboratory in a manner blinded to patient characteristics and outcomes. The result was positive: high resolution D was found to be a moderately robust predictor of arrhythmic death, with a relative hazard ratio of 0.79 for patients 1 SD apart in high resolution D. Importantly, high resolution D was specific for arrhythmic death but did not predict nonarrhythmic death. As with other data base–derived studies, the strength of conclusions is less than that inferrable from an entirely prospective study, and results should be regarded as preliminary and replicated in future studies.

Patients with and without events showed overlapping values for fractal D, suggesting that it may be useful primarily as a research tool or in conjunction with other factors as a clinical predictor. Also, D may be predictive only in a portion of the spectrum of postinfarction patients (i.e., in patients whose VPCs are "suppressible" [our randomized patient group] and not in those with greater cardiac dysfunction and nonsuppressible VPCs [our nonrandomized group]).

The ideal method of estimating fractal D is unknown. Although our high resolution algorithm for estimation of D appears to be an improvement over previous measures, it still has limitations, including a systematic overestimation of theoretic values. Additional refinements should be sought. Whether and to what extent fractal D is a true measure of "deterministic chaos" is not addressed in our report and is controversial (33). Currently, we view fractal D analysis as an innovative approach to signal processing of the ECG whose research value, clinical utility and mechanistic meaning remain to be fully determined. It should be recognized that the mechanisms influencing the distribution of VPCs in time and causing VPC clustering are unknown. The role of VPC clustering in triggering arrhythmic events, if any, is likewise unclear and will require further study. Nonetheless, fractal analysis, a

new approach to signal processing of the ambulatory ECG recording, appears to be promising, and further refinement and testing are indicated.

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